In recent years a possible role for bisphosphonates in the treatment of some rheumatic diseases has been proposed due to their anti-inflammatory properties. This can account for their observed efficacy in the relief of pain related to inflammation and bone marrow oedema in some rheumatic diseases (e.g. SpA and OA).

Complex regional pain syndrome type I (CRPS-I) is a severely disabling pain syndrome characterized by sensory and vasomotor disturbance, swelling, and functional impairment, in which neurogenic inflammation is acknowledged as one of the main pathophysiological mechanisms.

Over the past few decades, five randomized controlled trials (Table 1) and a number of open studies on the efficacy of bisphosphonates in the treatment of CRPS-I have been published. A recent randomized controlled trial showed that an amino-bisphosphonate, neridronate, is able to decrease pain and other clinical signs of the disease, as well as improve the functional status and quality of life of these patients [1].

Curiously, the literature offers more evidence of the efficacy of bisphosphonates in CRPS-I than any demonstration that osteoclasts, which are the main target of these drugs, are really involved in the physiopathology of the disease. Neither the studies on markers of bone turnover nor the few available histopathological investigations of bone in CRPS-I patients have demonstrated an enhanced osteoclastic activity, even in the first phases of the disease when bisphosphonates seem to exert the greatest efficacy. This apparent paradox suggests other mechanisms of action through which bisphosphonates can possibly exert their benefits in the treatment of this disease, beyond their well-known anti-osteoclastic properties.

Due to the high local concentration that bisphosphonates may reach at the site of the disease in CRPS-I (as can be inferred by the results of scintigraphic studies using a technetium-99 radiolabelled bisphosphonate as an i.v. marker) [2], these drugs could exert some mechanisms of action that are not active when bisphosphonates are used to treat other bone diseases.

The impressive reduction of local bone density in a few weeks after the onset of disease, which cannot be explained by an osteoclast-mediated process, is more probably related to a disturbance in mineralization, as demonstrated in diseases that share clinical and radiological features (e.g. transient osteoporosis of the hip) with CRPS-I. The chemical dissolution of hydroxyapatite crystals is probably induced by low local pH related to tissue hypoxia, increased anaerobic glycolysis and lactic acid concentration. In the pioneering phase of bisphosphonate research, one of the earliest effects proposed for the action of these drugs in the preservation of bone integrity was their ability to prevent hydroxyapatite crystal dissolution in an acid milieu when adequate drug concentrations were reached [3]. However, the therapeutic effect of bisphosphonates cannot be driven by only a structural preservation of bone architecture, and other mechanisms of action may be involved in counteracting pain and neurogenic inflammation. The local increase of lactic acid and the low pH in CRPS-I patients have been demonstrated to cause an antidromic release of calcitonin-gene-related peptide (CGRP) and substance P (SP) from nociceptive afferents, probably responsible for some manifestations of the disease, such as vasodilation, plasma extravasation, swelling and pain. It has long been known that bisphosphonates decrease lactic acid production from various cells [4].

Among the cellular lines involved in the physiopathological steps of CRPS-I, the mononuclear-phagocyte lineage locally activated by tissue injuries seems to exert a fundamental role, as can be inferred by the elevated blood levels of some proinflammatory subgroups of these cells [5]. Furthermore, macrophages together with other tissue cell lines contribute to the release of proinflammatory cytokines and nerve growth factor (NGF). NGF in turn promotes a further differentiation and activation of monocyte/macrophage lineage, increases the expression of some acid-sensing receptors in sensory neurons and induces the proliferation and activation of keratinocytes, a cellular line probably involved in maintaining inflammation, nociceptive sensitization and microvascular disturbances in CRPS-I. Bisphosphonates may interfere with this pathogenic pathway by an inhibition of proliferation, activation and viability of monocytes and macrophages [6], by decreasing the production of TNF-α and other proinflammatory cytokines [7] and by the inhibition of keratinocyte proliferation and growth [8].

Further possible mechanisms of action by which some bisphosphonates (namely amino-bisphosphonates) may interfere with the CRPS-I pathophysiology refer to the inhibition of farnesyl synthase and the post-translational modification of GTPases (Ras, Rab, Rho and Rac) involved in the function of G-protein-coupled receptors as a second messenger in the nociceptive signalling of...
### Table 1: Study characteristics of the five randomized controlled trials on bisphosphonates treatment vs placebo in CRPS

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Age, years</th>
<th>M/F</th>
<th>Disease duration</th>
<th>Post-traumatic, %</th>
<th>Intervention</th>
<th>Main results</th>
<th>Study duration</th>
<th>Follow-up, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adami et al., Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. Ann Rheum Dis 1997; 56: 201-4</td>
<td>20</td>
<td>Range 39-80</td>
<td>8/12</td>
<td>Range 5-34 weeks</td>
<td>80</td>
<td>Alendronate 7.5 mg i.v. daily for 3 days</td>
<td>VAS: -62% Tenderness improved Motion score improved</td>
<td>4 weeks</td>
<td>12</td>
</tr>
<tr>
<td>Varenna et al., Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome. A randomized, double blind placebo controlled study. J Rheumatol 2000; 27: 1477-83</td>
<td>32</td>
<td>55.6 (8.6)</td>
<td>13/19</td>
<td>4.0 (2.3) months</td>
<td>66</td>
<td>Clodronate 300 mg i.v. daily for 10 days</td>
<td>VAS: -62% Global clinical assessment improved Patient's perceived efficacy improved</td>
<td>40 days</td>
<td>12</td>
</tr>
<tr>
<td>Robinson et al., Efficacy of pamidronate in complex regional pain syndrome type I. Pain Med 2004; 5: 276-80</td>
<td>27</td>
<td>Mean 45 (range 30-60)</td>
<td>9/18</td>
<td>Mean 21.6 (range 3-72) months</td>
<td>N.R.</td>
<td>Pamidronate 60 mg i.v. in a single dose</td>
<td>VAS improved (P = 0.04) SF-36 improved Patient's global assessment improved</td>
<td>3 months</td>
<td>NR</td>
</tr>
<tr>
<td>Manicourt et al., Role of alendronate in therapy for posttraumatic complex regional pain syndrome type I of the lower extremity. Arthritis Rheum 2004; 50: 3690-7</td>
<td>40</td>
<td>Treated, 44.6 (12.3); placebo, 45.2 (12.5)</td>
<td>19/21</td>
<td>Treated, 7 (2) months; placebo, 8 (3) months</td>
<td>100</td>
<td>Alendronate 40 mg p.o. daily for 8 weeks</td>
<td>VAS: -67% Pressure tolerance improved Oedema decreased Joint mobility improved</td>
<td>8 weeks</td>
<td>NR</td>
</tr>
<tr>
<td>Varenna et al., Treatment of complex regional pain syndrome with neridronate: a randomized double-blind placebo-controlled study. Rheumatology 2013; 52: 534-42</td>
<td>82</td>
<td>Treated, 58.2 (12.7); placebo, 57.0 (10.3)</td>
<td>29/53</td>
<td>Treated, 4.7 (4.1) weeks; placebo, 5.0 (4.6)</td>
<td>65</td>
<td>Neridronate 100 mg i.v. every third day four times</td>
<td>VAS: -66% McGill pain questionnaire improved SF-36 improved Oedema decreased Passive motion increased Allodynia improved Hyperalgesia improved</td>
<td>40 days</td>
<td>14</td>
</tr>
</tbody>
</table>

Values are given as mean (s.d.) unless otherwise noted. SF-36: 36-item Short Form Health Survey; NR: not reported.
the peripheral sensory terminals. At this level, bisphosphonates may also act in a manner similar to some calcium blockers. Like nifedipine and tadalafil, which seem to reduce pain in CRPS-I patients by lowering cytosolic calcium concentrations, bisphosphonates could act by reducing the calcium influx through a local chelation of calcium ions [9], thus reducing hyperalgesia and allodynia and the local release of CGRP and SP. Finally, experimental studies suggest that bisphosphonates are able to prevent osteoblast and osteocyte apoptosis, regardless to the proapoptotic stimulus used [10], counteracting in this way one of the most frequent features reported in bone histopathological investigations in the early stages of the disease, bone cell apoptosis.

In summary, consistent with the results of most studies on this topic, bisphosphonates could be a useful therapeutic approach for CRPS-I patients, mainly in the early phases of the disease, when scintigraphic bone scans more frequently show local drug accumulation. This high local concentration perhaps represents the condicio sine qua non by which bisphosphonates exert some mechanisms of action that counteract the pathophysiological mechanisms of the disease. Consequently we can suppose that patients in whom scintigraphic scans are often negative, such as a long-standing disease or patients suffering from a primarily cold disease, could be unresponsive or less responsive to this treatment. With these limitations, bisphosphonates appear to present a therapeutic strategy that has been proved to reliably offer benefits in patients with CRPS-I.

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